2007, is considered timely. In lieu of an Appeal Brief, applicants are filing this Communication along with a Request for Continued Examination (RCE). The fee for filing an RCE is $395.00 and the enclosed check includes that amount. Accordingly, the RCE and this Communication are being timely filed

REMARKS

Claims 57-62 and 65-73 are pending and under examination in the subject application. Applicants have not added, canceled or amended any claims. Accordingly, claims 57-62 and 65-73 are still pending and under examination.

Rejection under 35 U.S.C. §101

The Examiner rejected claims 57-62 and 65-73 under 35 U.S.C. §101 as allegedly drawn to an invention with no apparent or disclosed specific, substantial and credible utility. Specifically, the Examiner alleges that the subject application does not identify a particular compound or class of compounds that activate or inhibit a Gr63F1 protein, nor does it disclose with specificity the consequence of that activation or inhibition.

In response, applicants respectfully traverse.

Briefly, the rejected claims provide isolated nucleic acids encoding insect gustatory and odorant receptor proteins and related compositions and methods. Gr63F1 is the elected species of such proteins. The value of the invention is dramatically underscored by the Nobel Prize awarded to inventor Richard Axel for the

discoveries underlying it.

As stated in their September 13, 2005 Amendment, applicants again maintain that the Examiner has erroneously concluded that the nucleic acids of the subject invention, and the receptors encoded thereby, are useless without knowledge of what compounds or class of compounds bind to the receptor or the consequences of that activation. Without conceding the correctness of the Examiner's remarks, applicants maintain that even without knowing which compounds or class of compounds bind to the claimed receptors, these receptors are useful. For example, the receptors can be used to screen for compounds which specifically bind to the receptor. Such screens are described in the specification at, *inter alia*, page 64, lines 22-31, and page 65, lines 10-19.

As stated in M.P.E.P. §2107.02(III)(A), "[i]n most cases, an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. 101." M.P.E.P. §2107.02(III)(A) further states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys, Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility." Applicants maintain that the Examiner has not provided any evidence that one of ordinary skill in the art would doubt that the claimed receptor would be useful in a screening assay.

M.P.E.P. §2107.02(II)(B) states that a claimed invention satisfies the utility requirement if it is known to have a well-established utility, i.e., if (i) a person of ordinary skill in the art would

immediately appreciate why the invention is useful based on the characteristics of the invention and (ii) utility is specific, substantial and credible.

Applicants assert that one of ordinary skill in the art would understand that the gustatory receptor Gr63F1 would have a specific, substantial and credible use without knowing the specific compounds that bind to it. In support of their position, applicants submit Kim, M., et al. ("The Invertebrate Odorant-binding Protein LUSH is required for Normal Olfactory Behavior in *Drosophila*", Chem. Senses 26:195-199, Feb. 2001) as **Exhibit A**. Kim, et al. describe experiments wherein flies lacking the gene encoding for the LUSH receptor, an odorant receptor having no previously known odorant ligand, were used to identify attractant compounds (See pages 196-197 of Kim, et al.). Specifically, Kim, et al. compared olfactory discrimination of 60 simple volatile organic compounds between *lush* mutants and wild-type adults using an olfactory trap assay. The results of the assay indicated a significant increase in the attraction of *lush* mutants to high concentrations of ethanol, propanol and butanol when compared to the control flies.

Applicants maintain that one of ordinary skill in the art would have understood that analogous experiments involving the Gr63F1 receptor could be performed, and that accordingly, the claimed invention possesses a specific, substantial and credible utility. Moreover, the receptors encoded by the claimed nucleic acids have a defined physiological function, i.e., gustatory receptor, and have use in identifying attractant compounds using known methodologies. Further elucidation of the gustatory receptors' function is not

required to establish their utility.

Rejection under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 57-62, 65-69, 71 and 72 under 35 U.S.C. §112, first paragraph, as allegedly failing to teach how to use the claimed invention (which applicants understand as an assertion that the specification does not teach a use for the claimed subject matter). The Examiner stated that the reasons for this rejection are the same as those set forth in support of the rejection under 35 U.S.C. §101.

In response, applicants direct the Examiner to their comments above and again maintain that both the usefulness of their invention and how to use them are taught, for the reasons set forth above. Accordingly, applicants request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph.

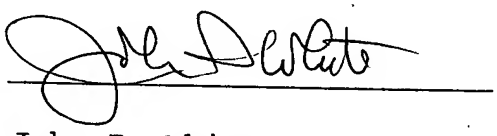
Summary

For the reasons set forth hereinabove, applicants maintain that the pending claims are in condition for allowance, and respectfully request that the Examiner concur.

No fee, other than the enclosed $395.00 fee for filing an RCE and the $1080.00 fee for a five-month extension of time, is deemed necessary in connection with the filing of this Communication and the accompanying RCE. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

Respectfully submitted,



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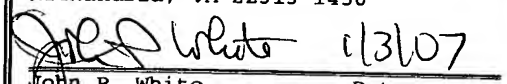

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EXHIBIT A

Chem. Senses 26: 195–199, 2001

The Invertebrate Odorant-binding Protein LUSH is required for Normal Olfactory Behavior in *Drosophila*

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Abstract

The invertebrate odorant-binding proteins consist of a large family of low-molecular-weight, highly divergent proteins expressed exclusively in the chemosensory sensilla of insects. Each member of this family studied to date is secreted into the sensillum lymph of a small subset of sensilla by non-neuronal support cells. These expression patterns suggests an odor-specific function for these proteins as opposed to a general role in sensillum biology. Consistent with this notion, mutants defective for LUSH, a *Drosophila* member of this family, have odor-specific defects in olfactory behavior. The *Drosophila* genome contains at least 32 members of this gene family, rivaling the number of odorant receptors in this species. The relationship between these two protein families and how they act to determine odor specificity of olfactory neurons will be the topic of future studies.

The molecular basis of olfactory detection and information processing is beginning to be understood. In vertebrate animals, millions of olfactory neurons are located in the nasal epithelium, overlaid by a thin layer of mucus. Odor specificity of vertebrate olfactory neurons appears to be determined by the odorant receptor expressed in the neuron (Buck and Axel, 1991; Zhou *et al.*, 1998; Malnic *et al.*, 1999). Each olfactory neuron expresses a single one of the 1000 or so odorant receptor genes and all neurons expressing the same receptor gene project their axons to the same glomerulus in the olfactory bulb (Vassar *et al.*, 1994; Sullivan *et al.*, 1995). The sensation of 'odor' is thought to result from the brain interpreting the pattern of glomerular activity in the bulb, which corresponds to the array of receptors activated at the periphery.

Non-neuronal support cells secrete a small number of vertebrate odorant-binding proteins (v-OBPs) into the mucus. The function of these proteins in olfaction is unknown. However, many odorants are hydrophobic molecules that have low aqueous solubility. Binding experiments show that v-OBPs bind odorants with a diverse array of molecular structures (Pelosi *et al.*, 1982; Pevsner *et al.*, 1985, 1990). These proteins are thought to increase the ability of hydrophobic molecules to enter the mucus layer [reviewed by Pelosi (Pelosi, 1995)]. Consistent with this notion, v-OBPs are members of the lipocalin family of hydrophobic molecule transporters that include transport molecules like the retinol-binding protein (Flower, 1996).

By contrast, the invertebrate odorant-binding proteins (i-OBPs) in insects are an independent gene family. Indeed, X-ray crystal structure data from the two types of OBPs reveal no structural relationship. v-OBPs bind odorants at the interface of a dimer (Bianchet *et al.*, 1996) while the i-OBPs bind ligand as monomers (Sandler *et al.*, 2000). Like the v-OBPs, the function of the i-OBPs are not known, but we have identified a mutant defective for a *Drosophila* i-OBP member. This mutant has odor-specific defects in olfactory behavior, implying a role for these proteins in olfactory discrimination and behavior.

The anatomy of the insect peripheral olfactory system is distinct from vertebrate and nematode olfactory model systems. In *Drosophila*, the 2000 or so olfactory neurons reside within segregated compartments called sensilla (Figure 1). Three morphologic classes of sensillum are present on the *Drosophila* antenna, including basiconic, trichoid and coeloconic sensilla [reviewed by Stocker (Stocker, 1994)]. All three classes detect odorants (Siddiqi, 1987; Clyne *et al.*, 1997), but the significance of the morphological differences is not known. Each sensillum is a hollow, hair-like structure filled with fluid called sensillum lymph that bathes the dendrites of the olfactory neurons contained within it. Each sensillum contains the dendrites of between one and four olfactory neurons. Different sensilla have different odor specificities (Siddiqi, 1987; Clyne *et al.*, 1997). While the recently discovered odor receptor gene products expressed in the olfactory neurons are likely to be major determinants of odor specificity for olfactory neurons in *Drosophila* (Clyne *et al.*, 1999; Gao and Chess, 1999;

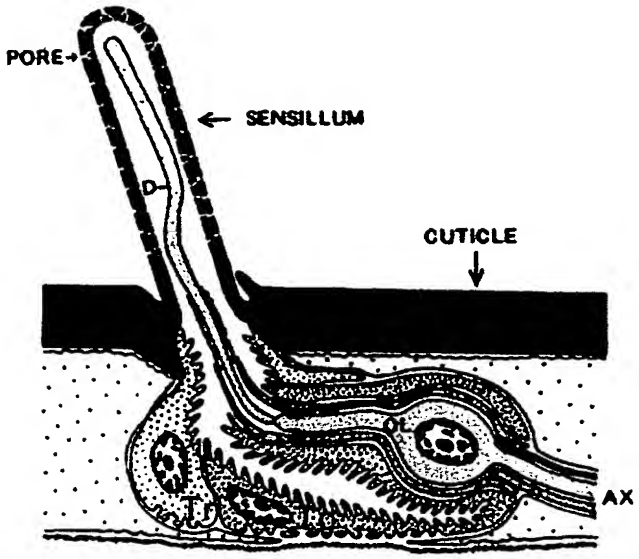

Figure 1 Insect sensillum. Olfaction is mediated by sensilla or sensory hairs located on the antenna. Odorants pass through pores in the sensillum cuticle to enter the sensillum lymph bathing the dendrites of the olfactory neurons. This fluid contains the repertoire of odorant-binding proteins, which varies between sensilla. Sensillum lymph is secreted by the trichogen (Tr) and tormogen (To) support cells. The thecogen support cell acts as a glial cell for the olfactory neuron. One to four olfactory neurons project dendrites into a single sensillum. [Modified from Farbman (Farbman, 1992).]

Vosshall *et al.*, 1999), there may be additional factors that modulate chemical specificity. Specifically, the segregation of neurons into sensilla provides insects with the opportunity to independently regulate components of the sensillar lymph which, in turn, regulate the concentration of odorants in the lymph, ultimately influencing the odor specificity of the neurons. The invertebrate OBPs are specifically secreted directly into the sensillum lymph. Some members are conserved across different *Drosophila* species (Hekmat-Scafe *et al.*, 2000), suggesting an essential role in olfactory function. Members of this family have been shown to directly bind odorant molecules (Vogt and Riddiford, 1981; Du and Prestwich, 1995; Sandler *et al.*, 2000). Furthermore, each member of the family is expressed in a small subset of sensilla, implying these molecules perform an odor-specific function (McKenna *et al.*, 1994; Pikielny *et al.*, 1994; Kim *et al.*, 1998). What is the function of the i-OBP family?

In *Drosophila* seven members of the i-OBP family have been reported, none of which are expressed in a sex-specific manner (McKenna *et al.*, 1994; Pikielny *et al.*, 1994; Kim *et al.*, 1998). Each *Drosophila* member is expressed in a subset of sensilla. We identified LUSH as a new *Drosophila* member of the i-OBP family using an enhancer trapping screen designed to identify genes expressed exclusively in the *Drosophila* antenna (Kim *et al.*, 1998). Briefly, a transposable genetic element containing the *LacZ* gene was randomly integrated into the *Drosophila* genome. Several thousand lines were generated, each containing a single transposon. Expression of the *LacZ* gene depends on acquiring local enhancer elements at the integration site to activate transcription of *LacZ*. Thus, the *LacZ* expression should mimic the expression pattern of endogenous genes located at the transposon integration site. Each transposon line was screened for β-galactosidase activity restricted to the antenna. One line integrated within 300 nucleotides of *lush*, the gene coding for LUSH.

LUSH has the hallmark features of a member of the i-OBP family, including olfactory-specific expression, a signal sequence for secretion from the non-neuronal support cells that secrete it into the lymph, and a series of six cysteines with conserved spacing (Raming *et al.*, 1990; Vogt *et al.*, 1991). Antiserum raised against LUSH protein confirmed that LUSH is secreted into the sensillum lymph of trichoid sensilla (Figure 2A).

While the existence of i-OBPs has been appreciated for >20 years, we still have little insight into the role of these proteins. Mutants defective for an i-OBP were not available. Having a transposon close to the *lush* gene provided an opportunity to generate the first OBP mutant. To create loss-of-function mutations in *lush*, we generated small deletions at the transposon integration site by 'jumping' the transposon out of the chromosome and screening for small local deletions. One deletion we recovered eliminated 3 kb of genomic DNA flanking the P element. This lesion completely removed the *lush* transcription unit, but did not appear to affect any other genes. Flies homozygous for this deletion are viable and fertile, and, as expected from the deletion, make no LUSH protein (Figure 2B).

To determine if the loss of a single i-OBP results in olfactory defects, we compared olfactory discrimination between *lush* mutants and wild-type adults using the olfactory trap assay (Woodard *et al.*, 1989). Briefly, 10 wild-type or mutant flies were placed in a Petri plate with a single odorant trap, and the number of flies within the trap was determined after a set time period. We screened a panel of 60 simple volatile organic compounds at different concentrations to test for differences in distribution between control and *lush* flies. Odorants were tested at 1:1000 and 1:4 dilutions in agarose. Comparing the responses of lush mutants with the strain carrying the transposon from which the mutants were derived minimized genetic background differences. These flies are expected to be genetically identical except for the presence of the transposon in the controls (which does not disrupt *lush* expression) and the lack of the *lush* gene in the experimental group. (Different strains of flies have dramatically different olfactory behavioral responses, making comparisons between hybrid strains uninterpretable.) Table 1 shows some of these data. As expected from the restricted expression pattern of LUSH in a subset of sensilla, the majority of the compounds attract similar proportions of wild-type and *lush* mutant flies, indicating that there is no global olfactory defect associated

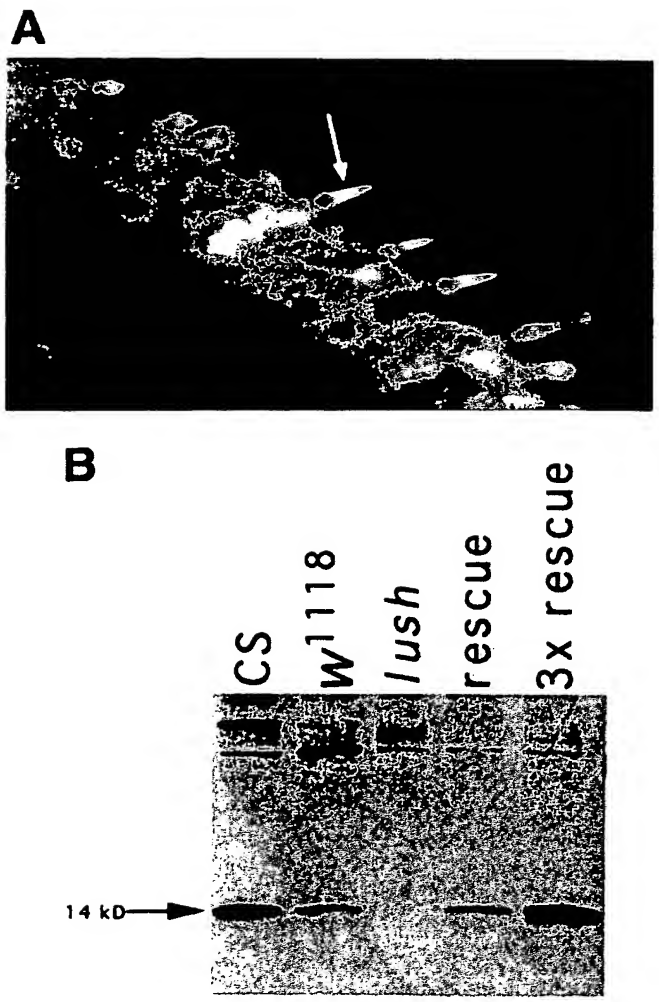

Figure 2 Expression of LUSH. **(A)** Anti-LUSH antiserum recognizes protein in support cells of trichiod sensilla. LUSH is present in the secretory system of the support cells and as soluble protein secreted into the sensillum lymph (arrow). **(B)** Western blot of antennal extracts from wild-type flies (*CS* and w^{1118}) and *lush* mutants (*lush*). The 14 kDa LUSH protein (arrow) is present in wild-type but not in *lush* mutants. Introduction of a wild-type copy of the *lush* gene under control of its own promoter into the *lush* mutants restores LUSH expression (rescue and 3× rescue).

Table 1 Olfactory behavioral responses of *lush* and control flies (w^{1118}) to a variety of odorants

Odorant	w^{1118}	*lush*	*P* value[a]
Ethanol			
1:1000	1.1 ± 0.45[b] (150)	0.8 ± 0.32	0.60
1:4	2.6 ± 0.55 (150)	5.6 ± 0.48	0.0002*
Propanol			
1:1000	2.7 ± 0.76 (100)	2.5 ± 0.68	0.85
1:4	0.1 ± 0.10 (100)	1.2 ± 0.25	0.0007*
Butanone			
1:1000	1.9 ± 0.34 (100)	1.1 ± 0.31	0.11
1:4	1.8 ± 0.47 (100)	1.8 ± 0.34	1.00
Acetone			
1:1000	2.3 ± 0.57 (100)	1.9 ± 0.50	0.41
1:4	2.5 ± 0.58 (100)	3.7 ± 0.76	0.23
Ethyl acetate			
1:1000	2.5 ± 0.50 (100)	1.9 ± 0.50	0.41
1:4	2.5 ± 0.61 (100)	2.1 ± 0.58	0.64
Isoamyl acetate			
1:1000	3.2 ± 0.42 (100)	2.7 ± 0.37	0.38
1:4	0.4 ± 0.22 (100)	0.5 ± 0.22	0.75
Acetic acid			
1:1000	4.6 ± 0.60 (100)	5.3 ± 0.70	0.89
1:4	1.1 ± 0.30 (100)	0.8 ± 0.20	0.23
Benzaldehyde			
1:1000	3.0 ± 0.73 (100)	2.7 ± 0.36	0.73
1:4	0.1 ± 0.09 (100)	0.0 ± 0.00	0.94
Yeast			
1:100	5.0 ± 0.60 (100)	4.7 ± 0.80	0.70

[a]*P* = The probability that the difference between the means for the two genotypes is the same by chance.

[b]Values are the mean number of flies (out of 10 possible) attracted to odorant traps. Numbers in parentheses indicate the total number of flies tested.

*Significant difference between genotypes (two-tailed *t*-test, independent samples).

with the loss of the *lush* gene. However, odor-specific defects in chemosensory behavior are observed in *lush* mutant flies when challenged with three chemically related odors. We observed a significant increase in the number of mutant flies in traps containing high concentrations of ethanol, propanol and butanol compared with control flies. Responses to a variety of other alcohols are not different to the wild type. Interestingly, the apparent increased attraction of *lush* flies for ethanol, propanol and butanol is specific to high odorant concentrations (Figure 3A). Figure 3B reveals the dose-dependent, abnormal attraction of *lush* mutants for ethanol. *lush* flies are attracted to yeast extract, ethyl acetate and low concentrations of ethanol to a similar extent as the wild type. However, the mutant flies display an abnormal attraction to traps containing high concentrations of ethanol (Figure 3B, 1:100, 1:4). We named this deletion mutant '*lush*' to reflect their increased affinity for ethanol-rich environments. We conclude that *lush* mutants have odor-specific defects in chemosensory behavior and are abnormally attracted to high concentrations of a subset of odorants, including ethanol, propanol and butanol.

The increased likelihood of *lush* mutant flies to enter traps containing high concentrations of these alcohols could result either from increased attraction to these odorants or from a defect in avoidance of high concentrations of these compounds. If there is a defect in chemoavoidance to ethanol in *lush* mutants, we should be able to demonstrate this behavioral response in wild-type flies. To determine this, we tested the effects of mixing ethanol with yeast extract, a strong chemoattractant. Figure 3C shows that wild-type

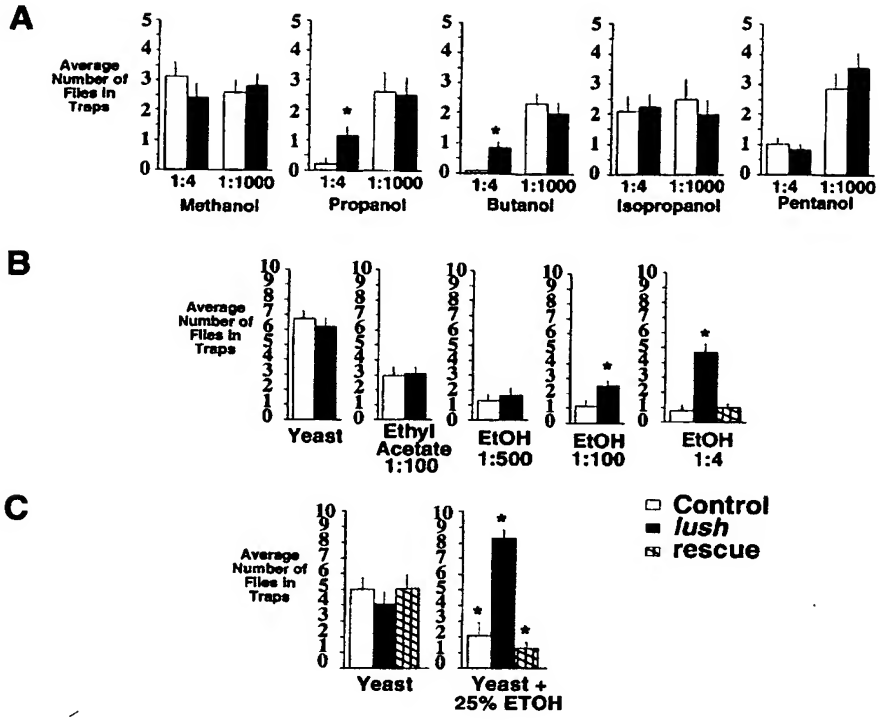

Figure 3 Olfactory behavioral responses of wild-type and *lush* mutant flies. **(A)** Olfactory trap assay data for short chain alcohols. The number of flies entering traps is denoted on the *y* axis, the concentration of odorant in agarose is denoted on the *x* axis. *lush* mutants (black bars) have abnormal olfactory behavioral responses to high levels of ethanol, butanol and propanol compared with controls (white bars). An asterisk denotes statistical significance. **(B)** Dose–response data for *lush* mutants, wild-type control flies and *lush* mutants transformed with a wild-type copy of the *lush* gene (hatched bars). *lush* mutants have a dose-dependent abnormal affinity for traps containing concentrated alcohol. Wild-type behavior is restored by a transgenic copy of *lush*. **(C)** Wild-type flies have endogenous mechanisms to avoid concentrated ethanol that are defective in *lush* mutants. Dilute yeast extracts attract equivalent numbers of wild-type, *lush* mutants, and *lush* mutants transformed with a wild-type *lush* transgene. The addition of 25% ethanol reduces the attraction of the yeast for wid-type flies (white bars). *lush* mutants are not repelled by concentrated ethanol as are normal flies, and find the mixture highly attractive (black bars). The introduction of a *lush* transgene into the mutants restores wild-type behavior (hatched bars).

flies are attracted to dilute yeast extract (left panel, open bars). However, when the same amount of yeast is mixed with 25% ethanol, wild-type flies are significantly less likely to enter these traps (compare open bars). Therefore, the presence of high levels of ethanol reduces the attractiveness of the yeast for wild-type flies. This demonstrates that there is an active avoidance mechanism in wild-type flies that is stimulated by high concentrations of ethanol. *lush* mutants are equally attracted to yeast as wild-type flies (filled bar, left graph) but are defective for the avoidance behavioral response (Figure 3C, filled bars). In fact the *lush* mutants are significantly more attracted to the mixture of yeast and concentrated ethanol than to yeast alone. These results are consistent with the notion that neurons within the sensilla expressing LUSH mediate avoidance to concentrated alcohols and that LUSH is important for the activity of these neurons. However, alternative models are also consistent with these data. For example, the LUSH-positive sensilla may contain olfactory neurons that mediate attraction to alcohol, and LUSH normally functions to remove alcohol from the lymph when the levels get very high.

To prove that the chemosensory defects we observed in the *lush* mutants are due entirely and specifically to loss of LUSH protein in the trichoid sensilla, we introduced a cloned wild-type copy of this gene under control of its own promoter into *lush* mutant flies by germline transformation. Expression of a *lush* transgene under control of its own promoter in the mutant background restores LUSH expression to normal levels (Figure 2B, Rescue). Furthermore, the transgene completely restores wild-type olfactory behavioral responses to the *lush* mutants (Figures 3B, striped bars). Therefore, the abnormal chemoattraction of *lush* mutants to high levels of alcohol results specifically from loss of LUSH protein in a small subset of trichoid sensilla. We conclude that *lush* mutants have defective chemosensory responses to a subset of odorants resulting from loss of a single odorant-binding protein in the sensillum lymph of a small subset of trichoid chemosensory sensilla.

Future prospects

There are ~60 odorant receptors in the *Drosophila* genome (Vosshall *et al.*, 2000). We have scanned the *Drosophila* genome for candidate odorant-binding proteins and have identified 25 new potential members of this family, making the total number of potential *Drosophila* odorant-binding proteins to 32 (D.P. Smith, unpublished data). The challenge for the future will be to determine how these molecules function at the biochemical level to influence olfactory behavior.

Acknowledgements

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